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First-in-Human study of CH5132799, an Oral Class I PI3K Inhibitor, Studying Toxicity, Pharmacokinetics and Pharmacodynamics, in Patients with Metastatic Cancer

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Abstract

Purpose—This Phase I dose-escalation study investigated the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary clinical activity of CH5132799.

Patients and Methods—Patients with metastatic solid tumors were eligible for the study. CH5132799 was administered orally once daily (QD) or twice daily (BID) in 28-day cycles.

Results—Thirty-eight patients with solid tumors received CH5132799 at 2-96 mg QD or 48-72 mg BID. The MTD was 48 mg on the BID schedule but was not reached on the QD schedule. DLTs were grade 3 elevated liver function tests (LFT), grade 3 fatigue, grade 3 encephalopathy, grade 3 diarrhea and grade 3 diarrhea with grade 3 stomatitis; all DLTs were reversible. Most

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drug-related adverse events were grade 1/2. Diarrhea (34%) and nausea (32%) were the most common events. Mean C_{max} and AUC_{0-24} in steady state at MTD were 175 ng/ml and 1,550 ng·hr/ml respectively, consistent with efficacious exposure based on preclinical modelling. Reduction in SUV_{max} with [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) was observed in five of seven patients at MTD. A patient with *PIK3CA*-mutated clear cell carcinoma of the ovary achieved a partial response by GCIG CA125 criteria and further, a heavily pre-treated patient with triple negative breast cancer had marked improvement in her cutaneous skin lesions lasting 6 cycles.

Conclusion—CH5132799 is well tolerated at the MTD dose 48 mg BID. At this dose the drug had a favorable PK and PD profile and preliminary evidence of clinical activity.

Keywords

Phase I; Class I PI3K inhibitor; CH5132799; dose-escalation; advanced/metastatic solid tumors

Introduction

The intracellular phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway regulates cellular functions such as cell survival, proliferation, growth, apoptosis, protein synthesis and glucose metabolism (1-6). Of the three classes of PI3K (I to III), class IA is implicated most in cancer (5). Class IA PI3K heterodimers comprise a p85-regulatory and a p110-catalytic subunit with several isoforms (5). Mutation or amplification of *PIK3CA*, the gene encoding the catalytic subunit of PI3K (p110α), promotes oncogenic activation of the PI3K pathway and occurs frequently in human cancers such as ovarian cancer and breast cancer (1, 6-12). Phosphatase and tensin homolog (PTEN), a key negative regulator of AKT, can be inactivated via mutations, down-regulation, or loss of protein expression, and is associated with tumorigenesis in prostate, gastric and other cancers (1, 13-19). Moreover, it is likely that PI3K pathway activation is associated with resistance to both chemotherapy (20-22) and targeted agents (23-26). Selective inhibition of the PI3K/AKT/mTOR pathway in cancer represents a promising therapeutic approach and has been the focus of significant research efforts including the clinical development of novel agents targeting this pathway (1, 19, 27-37).

CH5132799 (Chugai Pharmaceutical Co Ltd, Tokyo, Japan) is an oral PI3K inhibitor with specific and potent activity against class I PI3Ks, especially demonstrated in wild-type and mutant PI3Kα isoforms, and PI3Kγ at nanomolar concentrations(38). CH5132799 has no inhibitory activity against class III PI3K, or mammalian target of rapamycin (mTOR) (38). In vitro experiments demonstrated a strong antiproliferative effect of CH5132799 on human cancer cell lines with alterations in the PI3K pathway (38, 39). In vivo, CH5132799 demonstrated significant antitumor activity in human tumor xenograft models with *PIK3CA* mutations, with good correlation between CH5132799 exposure and inhibition of PI3K signalling (39).

The primary objective of this first-in-human, Phase I, dose escalation study was to determine the MTD of CH5132799 using a continuous oral schedule in patients with advanced solid tumors. Secondary objectives included the characterisation of CH5132799 PK, and the PD

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profile of PI3K inhibition in tumor and in surrogate tissues such as peripheral blood samples, and by [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET).

Patients and Methods

Study population

Patients had been diagnosed with advanced solid tumors that were not amenable or were refractory to standard therapy. Patients were aged ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and adequate bone marrow, renal, hepatic and cardiac function were enrolled (see supplementary data for detailed inclusion and exclusion criteria) and a life expectancy of ≥12 weeks.

This study was approved by an independent ethics committee (The Royal Marsden Research Ethics Committee, London, United Kingdom) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). Written informed consent was obtained from all patients before carrying out any study-related procedures.

Study design and CH5132799 dose escalation

This open-label dose-escalation study was conducted at four centers. Prior to the first treatment cycle, CH5132799 was administered as a single oral dose followed by a 5–7 day washout (run-in period). A classical “3+3” design was used for dose-escalation with QD to the early patient cohorts, and then BID to others, continuously in 4-week cycles. Dose escalation was determined by the nature and grade/severity of toxicities.

The primary objective was to determine the MTD of CH5132799 based on DLTs observed during the run-in period and first 4-week cycle. The MTD was defined as the highest dose level at which no more than one of six patients experienced a DLT. A starting dose of 2 mg was chosen based on the highest non-severe toxic dose in a non-rodent species and the severely toxic dose (10% lethal dose) in rat, which means 7.8-fold and 30-fold safety margins were applied to the two metabolically/kinetically relevant animal species, respectively (40).

Assessments

Medical history and demographic data were collected at baseline. Physical examination, monitoring of vital signs and other safety assessments were performed throughout the study. All toxicities were documented using Common Terminology Criteria for Adverse Events (CTCAE) V4.03 (41). DLTs were defined as grade ≥3 non-hematologic toxicity despite adequate treatment, grade 4 neutropenia lasting ≥7 days, febrile neutropenia, grade 4 thrombocytopenia lasting ≥7 days or requiring a platelet transfusion.

Tumor response was assessed according to Response Evaluation Criteria In Solid Tumors (RECIST; version 1.1) with imaging at baseline and every two cycles (42).

Pharmacokinetics and Pharmacodynamics

Plasma PK samples were collected on Cycle 0, Day 1, followed by Cycle 1, Days 1, 8, 15 and 22. Plasma concentrations of CH5132799 were measured by a validated LC/MS/MS assay method (Chugai Pharmaceutical Co. Ltd., Kamakura, Japan, data on file) and PK parameters calculated by non-compartmental analysis with first-order oral absorption (WinNonlin Ver 5.3 and Phoenix WinNonlin Ver.6.1 (Pharsight Corporation, NC, USA). The CH5132799-related inhibition of AKT phosphorylation (pAKT) was studied in platelet-rich plasma (PRP). Blood for PRP samples was collected at 0 (pre-dose), 1, 2, 6, 24, 48 and 72 hrs post-dose on Day 1 of the run-in period (Cycle 0, Day 1) and at 0 (pre-dose) on Cycle 1, Day 15. Blood samples were collected into BD Vacutainer sodium citrate coagulation tubes and centrifuged at 200 × g at 4°C for 15 minutes. The isolated PRP layer was incubated with PhosSTOP (Roche) to stabilize the phosphorylation signals and then lysed using Cell Lysis Buffer (Cell Signaling Technology) containing phenylmethane sulfonyl fluoride (Sigma-Aldrich) and then snap-frozen on dry ice. PD analysis with PRP was performed by The Institute of Cancer Research. All PRP samples were analysed for the levels of phosphorylated and total forms of PD biomarker AKT by a Meso Scale Discovery® electrochemiluminescent assay (ECLA). The assay was modified into a GCP-compliant quantitative assay for AKT by inclusion of a standard curve of recombinant active AKT protein on every plate. The quality, accuracy and precision of the assays were monitored using quality control (QC) samples created by spiking three known quantities of recombinant AKT into 10% human plasma.

Biopsies were performed at screening and at Cycle 1, Day 15. Flash frozen tumor biopsies were homogenized using a micro tissue grinder in Cell Lysis Buffer (w/v) containing PhosSTOP. The tumor lysates were centrifuged to remove debris and the protein concentration measured using the BCA assay (Pierce). Tumor biopsy samples were analysed for the levels of phosphorylated and total forms of PD biomarker AKT by a quantitative ICR modified GCP compliant Meso Scale Discovery® electrochemiluminescent assay (ECLA). [^{18}F] Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging was performed within 28 days prior to the first dosing of CH5132799, Cycle 1, Day 8, and Cycle 3, Day 1. Lesions with the highest degree of FDG uptake were selected for quantitative analysis and a circular/spherical region of interest drawn. A SUV_{max} was measured for each selected lesion and the delta change in SUV_{max} was calculated. Tumor biopsies were taken after FDG-PET scanning to avoid interference of biopsy on FDG uptake.

Detection of mutations

PIK3CA/*KRAS*/*BRAF* mutations were studied with the OncoCarta panel v1.0 and detected by mass ARRAY System.

Statistical analyses

Descriptive statistics were used for the analysis of PK, PD, safety and tumor response data.

Results

Thirty-eight patients received at least one dose of CH5132799 (Table 1), of whom 23 received CH5132799 QD (2-96 mg/day). The decision to dose BID was made as there had been no DLTs and no significant increase in drug concentrations at doses above 56 mg QD along with PD measures i.e. recovery of p-AKT after 12 hours. Subsequently 15 further patients then received CH5132799 BID (96–144 mg/day). Overall, patients received a median of 2 cycles (range 0–6), with a median duration of 52 days of treatment (range 1–164 days). Archival tumor samples were available in 30 patients. *PIK3CA* mutations were found in 10% (3/30) of samples studied (Table 1).

Dose-limiting toxicities

DLTs were observed in five of 38 evaluable patients who received CH5132799 BID and completed the first cycle (Table 2A). Of seven patients at 48 mg BID, one patient with hepatocellular carcinoma experienced grade 3 elevated transaminases. Although the patient had liver metastases with elevated LFTs (grade 2) at baseline, a causal link to CH5132799 could not be excluded because clear evidence of disease progression in liver metastasis was not observed. At the next dose level, two of three patients receiving 72 mg BID had DLTs. One had grade 3 fatigue that was resolved following cessation of CH5132799 and she restarted CH5132799 with reduced dose when fatigue had been resolved and she did not experience the event later on, whilst the other developed grade 3 posterior reversible encephalopathy syndrome (PRES) that was presented with seizures. The diagnosis was made on characteristic MRI findings and the symptoms resolved on cessation of CH5132799 as well as instigation of supportive care without restarting CH5132799. Two of five patients receiving the intermediate dose of 56 mg BID had grade 3 diarrhea, the other grade 3 diarrhea with grade 3 stomatitis, which resolved following cessation of CH5132799 and instigation of supportive treatment, in both cases study treatment was then restarted at a reduced dose without further DLTs. Therefore, the MTD and recommended phase 2 dose (RP2D) of CH5132799 administered orally was established at 48 mg BID.

Safety

The most common AEs were: diarrhea, nausea, stomatitis, fatigue, and rash which occurred in 68%, 32%, 32%, 29% and 24% of patients, respectively (Table 2B). Diarrhea was predominantly grade 1 or 2, with no grade 4 diarrhea reported. Four patients experienced grade 3 diarrhea (96 mg QD, n=2; 56 mg BID, n=2). One patient experienced grade 3 nausea (96 mg QD). No grade ≥3 gastrointestinal AEs occurred in the cohort who received CH5132799 at the R2PD (48 mg BID). Hyperglycemia was predicted due to the mechanism of action of CH5132799. Five patients experienced Grade ≥3 hyperglycemia in the BID dosing schedule suggesting a dose-dependent effect (48 mg BID, n=1; 56 mg BID, n=2; 72 mg BID; n=2 including one Grade 4). No episodes of diabetic ketoacidosis occurred and hyperglycemia was controlled with oral metformin as required. No drug-related deaths were reported.

Pharmacokinetics

Following oral administration of a single dose of CH5132799, plasma concentrations peaked with a T_{max} at 2.60 hours and $t_{1/2}$ of 10.2 hours at the MTD (Figure 1A). Dose proportionality of AUC was shown in the dose range of 2 to 56 mg (Figure 2B). Steady state was reached by Cycle 1, Day 8 at the latest with little subsequent accumulation; there was no further increase in AUC at higher doses. At the MTD of 48 mg BID, mean C_{max} and AUC_{last} were 172 ng/mL and 1,270 ng·hr/mL after a single dose, respectively. Mean C_{max} and $AUC_{0\text{-}24h}$ were 175 ng/mL and 1,550ng·hr/mL at steady state, respectively (Table 3).

Pharmacodynamics

Significant inhibition of PI3K signalling was observed in PRP, with reduction of AKT phosphorylation at doses of 32 mg and above (Figure 2A). The temporal relationship between reduction in phosphorylation of AKT and dosing administration with CH5132799 suggested target engagement for less than 24 hours (Figure 2B). This observation contributed to the decision to increase dosing frequency to BID.

Pre- and post-treatment tumor biopsies were optional and the minimum number to be conducted during the study was not based on statistical assumptions. Tumor biopsy samples were collected before and after CH5132799 from three patients (one patient each on 56 mg QD, 96 mg QD and 56 mg BID). There was a more than 50% reduction in normalized p-AKT levels in two of the three patients (Figure 2C).

A decrease in FDG avidity between baseline and Cycle 1, Day 8 was observed in 74% of patients (17/23) who underwent serial PET imaging (Figure 2D). It was interesting that five of seven patients at the RP2D who had pre-and post- (Cycle1, Day 8) treatment PET scans showed a reduction in maximum standardised uptake value (SUV_{max}); two had a reduction in SUV_{max} of 55% and 44%.

There was no correlation between the PD changes in the limited number of biopsies, PET responses or PRP inhibition.

Efficacy

There were no RECIST partial or complete responses but one patient with *PIK3CA H1047R*-mutated clear cell ovarian cancer had a GCIG CA125 response having been treated at 48 mg BID and remained on study for 6 cycles (Figure 3A). A second patient with heavily pre-treated triple negative breast cancer bearing no *PIK3CA* or *AKT* mutations who was treated at the 72 mg BID dose level had marked symptomatic and objective improvement in her cutaneous skin lesions and remained on treatment for 6 cycles (Figure 3B). Disease stabilisation was seen in eight patients up to week 16 (approximately 4 cycles), including two patients with *PIK3CA* mutation.

Discussion

We report the first-in-human study of an oral PI3K class I inhibitor CH5132799. No DLTs occurred at the QD schedule, but the BID schedule was selected based on the duration of target inhibition observed in platelet-rich plasma and the lack of dose dependent incremental

elevation in concentrations of drug above 56 mg QD. The BID schedule of CH5132799 was well tolerated and showed evidence of clinical and PD activity with a RP2D of 48 mg BID.

The most frequently observed toxicities were gastrointestinal, including diarrhea, nausea and stomatitis. These have been described previously in studies of PI3K, AKT and m-TOR inhibitors (28, 30-38). Reversible grade 3 LFT elevation was observed in one of seven patients treated at the MTD of 48 mg BID. This patient with hepatocellular carcinoma had liver metastases and had previously undergone hepatic resection, therefore the event was possibly caused by disease progression and/or overload of a liver with insufficient metabolic capability. No other cases of drug-related LFT abnormalities were noted although they have been described in trials of other PI3K inhibitors (30-32, 34, 43). Of note, we observed one case of PRES at a dose above the MTD. This has not been reported previously in the trials of other drugs in this class, nevertheless, it raised the possibility that CH5132799 crosses the blood-brain barrier, which may be of future relevance in the treatment of patients with intracerebral malignancies. Mood alterations have been described as adverse events in with other PI3 kinase inhibitors (30, 43), however was not seen in this trial. Although skin-related toxicities have been frequently observed in the trials of other PI3K inhibitors (28-30, 32, 33, 35-37, 43-45), CH5132799 was associated with only mild to moderate skin toxicities at a lower frequency. On-target toxicity such as hyperglycemia was observed with CH5132799 as with other PI3K, AKT and m-TOR inhibitors (28-30, 35-37, 44, 45) although did not result in ketoacidosis was well-controlled by metformin. The favorable toxicity profile of CH5132799 may make it suitable to combine with other targeted agents such as epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) or MAPK/ERK kinase (MEK) inhibitors.

The PK data show it was possible to attain CH5132799 concentrations in patients that had been efficacious in xenograft models(39). The AUC increased proportionally with dose from 2-56 mg. The PD data indicated target modulation using phosphorylation of AKT at Sr473 as a proof of mechanism biomarker. Levels of p-AKT were reduced in PRP consistently at dose levels 8 – 96 mg. The maximal inhibition approximately 50% compared to baseline and this was achieved at dose levels of 32 mg. p-AKT levels in PRP frequently recovered by 24 hrs following treatment. The duration of PD biomarker changes in normal tissue and the fact that there were no significant further reduction in p-AKT levels after the 32 mg cohort, along with the fact that the AUC of CH5132799 did not rise significantly above 56 mg, led us to explore a twice-weekly schedule, despite not reaching an conventional MTD at 96 mg on the once-daily dosing cohorts. At the recommended phase II dose of 48 mg BID levels of p-AKT were reduced in PRP and in a limited number of post-treatment tumor biopsies. There was a reduction in levels of p-AKT (Ser473) in 2/3 tumor at the higher dose levels but there was considerable variation in reduction between patients (Figure 2c). The degree of p-AKT reduction in the tumor from patients were less than what was seen in xenograft models (39), however this could reflect different platforms to assess AKT phosphorylation and other factors such as intra-tumoral heterogeneity.

Further evidence of tumor target modulation was observed with FDG-PET scans with all patients at recommended dose. All five patients scanned at the RP2D having a reduction in SUV_{max} and two of them achieved a PET response by PERCIST criteria (46). Although the

number of patients is too small to draw definitive conclusions, these PD data are highly encouraging. There was no correlation between the PD changes in the limited number of biopsies and PET responses or PRP inhibition. The FDG PET was done pre-treatment and on day 8 of treatment while tumor biopsies were performed pre-treatment and day 15 of treatment while the detailed p-AKT studies in PRP were done on day 1 of treatment. The small number of biopsies and the disparities in the days when tests were conducted could have led to the lack of correlation between p-AKT levels in tumor, PRP and changes in SUV_{max} on PET.

The eight study participants (21%) showing a best response of stable disease by RECIST included two participants who with clear clinical responses. In reports of other PI3K, AKT and mTOR inhibitors as single agent in patients with solid tumors, disease stabilization was observed, but only a few cases of radiological response have been reported (28-32, 34-36, 44). Therefore, there was clinical evidence as well as PD activity for CH5132799. These results indicated that CH5132799 was comparable to other PI3K, AKT and m-TOR inhibitors in terms of single agent activity.

Three patients were found to have *PIK3CA* mutations. Although there were no objective radiologic responses, it was interesting that one of these patients (with clear cell ovarian cancer) had a GCIG-defined partial response in her CA125 tumor marker. Another patient with triple negative breast cancer had a visible response in cutaneous metastases. This patient with breast cancer did not have any *PIK3CA* mutation, although triple negative breast cancer was known frequently to diseases associated with other perturbations in PI3K pathway (47). Pre-clinical models suggest that *PIK3CA* mutations predict for sensitivity to PI3K inhibitors as either single agents (48, 49) or in combination (50). This was also seen with preclinical studies of CH5132799(39). However, the clinical correlation of between *PIK3CA* mutations and PI3K inhibitors to this has not been fully realised (51) in the clinic and it is possible that other activating mutations (52) or intra-tumoral heterogeneity (53) may play a role.

We conclude that CH5132799 at RP2D of 48 mg BID is well tolerated and attains drug concentrations which show evidence of achieving target engagement in both normal tissues and tumor. CH5132799 has clinical as well as PD activity which was one with evidence of proof-of-mechanism from a clinical response in one patient with *PIK3CA* mutant ovarian cancer patient. The favorable toxicity profile and activity observed with single-agent CH5132799 suggests it is suitable for combination with other targeted therapies, and for exploration in subsets of patients with cancers harboring pre-defined mutations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Translational Relevance

CH5132799 is an oral pan-PI3 kinase inhibitor designed to target both alpha and beta isoforms of PI3K, which are frequently deregulated in cancer due to activating mutations in the oncogene *PIK3CA* or loss of function of the tumor suppressor gene, *PTEN*. The dosing schedule was to be determined by toxicity, PK and PD parameters and started with a QD schedule followed if necessary by a BID schedule. The trial started with CH5132799 administered orally once a day (QD) but a formal MTD was not reached at 96 mg however as there were no significant increments in AUC above a dose of 56 mg QD and p-AKT showed recovery at 24 hrs. Therefore, the dosing schedule was modified to include twice a day dosing (BID). A dose of 48 mg BID was declared the recommended phase II dose, at which dose a patient with *PIK3CA* mutant clear cell ovarian cancer responded.

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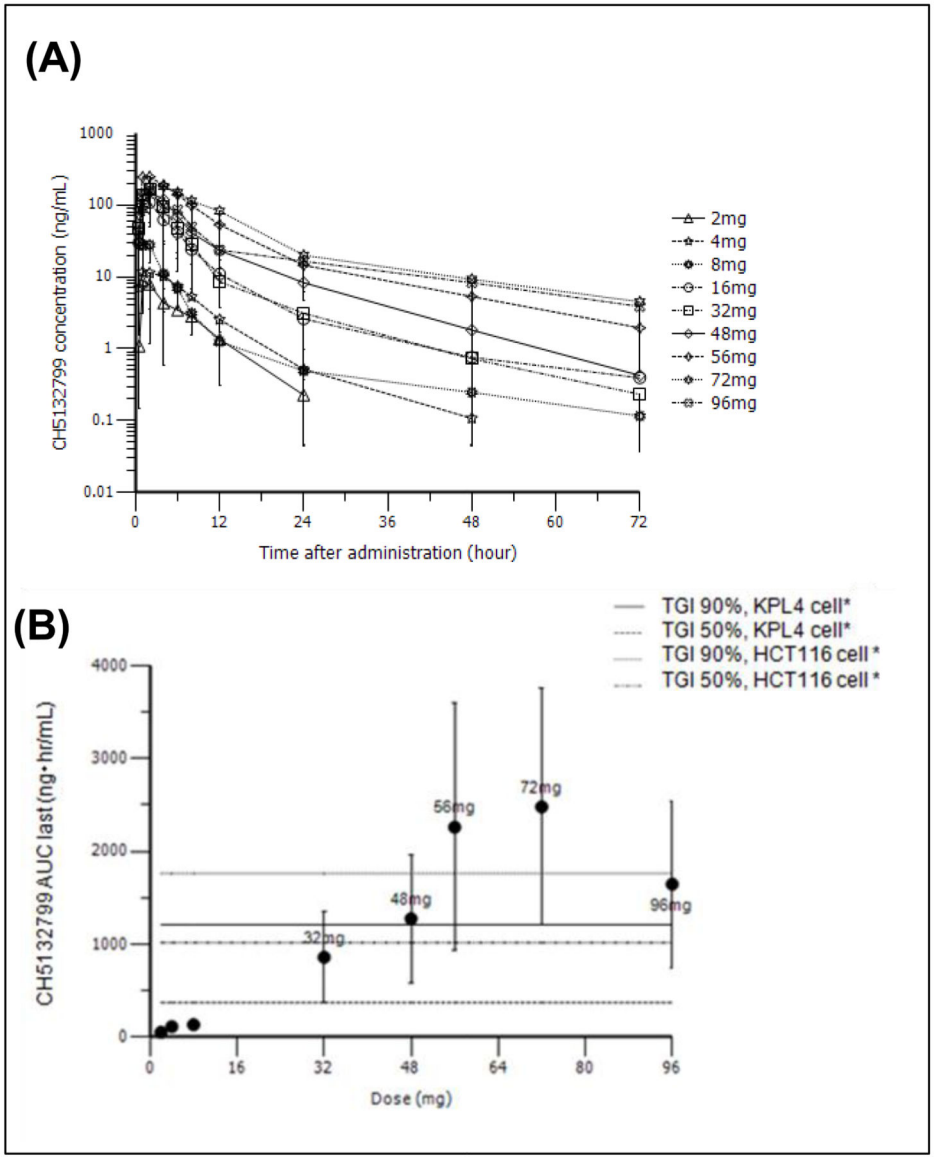

Figure 1. Pharmacokinetic parameters of CH5132799

A) Plasma concentration of CH5132799 following a single administration across the dose range of 2 mg – 96 mg. B) The correlation of the AUC (area under the curve) of CH5132799 and dose. The horizontal lines indicate effective AUC calculated to cause TGI (tumor grown inhibition) of 50% and 90% of the KPL4 and HCT116 xenograft models.

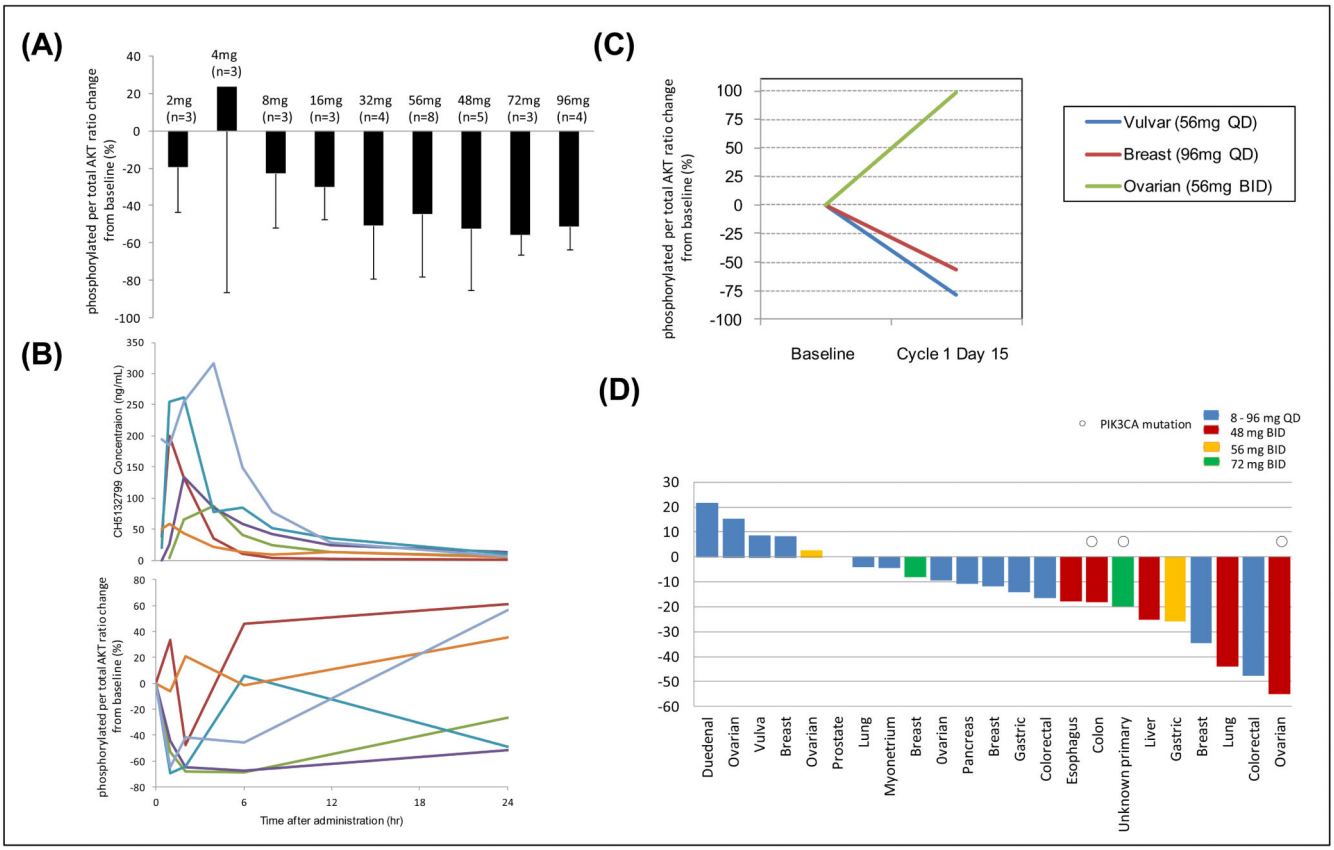

Figure 2. Pharmacodynamic parameters of CH5132799

A) Mean percentage change of phosphorylated AKT normalized to total AKT compared to pre-treatment control values, 2 hrs following a single dose of CH5132799. B) The temporal course of plasma concentration of CH5132799 and the percentage change of p-AKT normalized to total AKT compared to pre-treatment control values following a single dose of the recommended phase II dose of CH5132799 (48 mg). C) Percentage change of p-AKT normalized to total AKT in tumor biopsies when compared to pre-treatment samples. D) SUV_{max} changes on FDG-PET scans in patients who had evaluable pre- and post-treatment FDG-PET scans.

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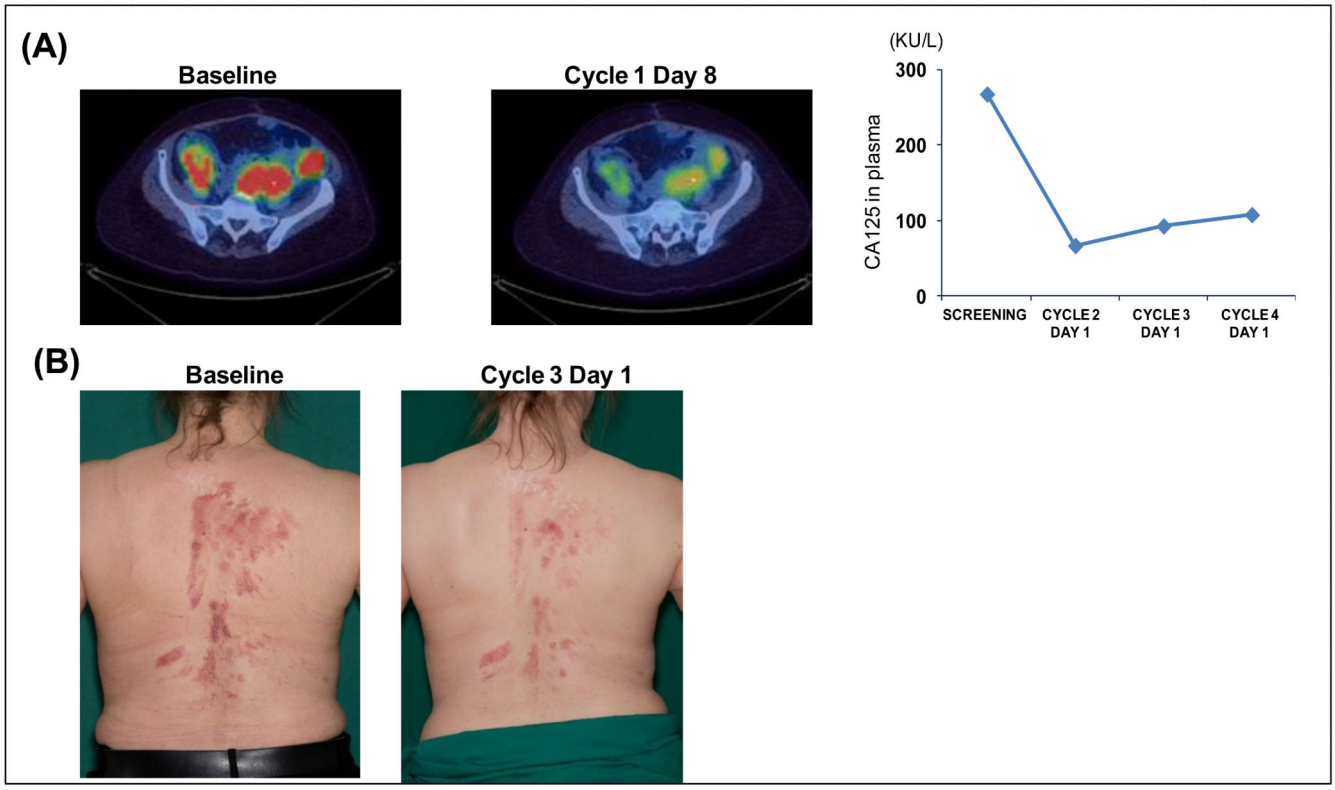

Figure 3. Clinical efficacy of CH5132799

A) FDG-PET-CT showing reduction in uptake of tracer in pelvic masses and a reduction of CA125 following treatment with CH5132799. The patient had a clear cell ovarian cancer which harbored a *PIK3CA* mutation. B) Representative skin lesions, before and after treatment with CH5132799, of a patient with triple-negative breast cancer.

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Table 1
Patient demographics and clinical characteristics

Characteristic	Total patients (N=38)
Sex	
Male	10 (26%)
Female	28 (74%)
Age, years	
Median	58.5
Range	41-76
Race	
Asian	3 (8%)
Black	3 (8%)
White	32 (84%)
Baseline ECOG performance status	
0	12 (32%)
1	25 (66%)
2	1 (3%)
Prior anti-cancer therapies, median (range)	3 (1–8)
Primary tumor site and mutational status	
Breast	10 (26%)
No mutation	8
Unknown mutational status	2
Ovarian	6 (16%)
KRAS G12D	1
PIK3CA H1047R	1
No mutation	3
Unknown mutational status	1
Oesophageal and oesophageal-gastric adenocarcinoma	5 (13%)
KRAS G12D	1
EGFR S768I	1
No mutation	3
Duodenal and large intestine	4 (11%)
KRAS G12A	1
KRAS G12D and PIK3CA E545K	1
No mutation	2
Gastric*	2 (5%)
Lung*	2 (5%)
Endometrial*	1 (3%)
Vagina*	1 (3%)
Myonetrium*	1 (3%)
Vulva*	1 (3%)
Bladder*	1 (3%)
Pancreas*	1 (3%)
Prostate*	1 (3%)
Unknown primary origin	1 (3%)
PIK3CA E545K	1

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Table 2 A

Dose limiting toxicities seen on the study

Cohor	Dose	N	DLT 1
7b	48 mg BID	7	grade 3 elevated LFT at Cycle 1 Day 8
8	72 mg BID	3	grade 3 cerebral encephalopathy at Cycle 1, Day 14 grade 3 Fatigue at Cycle 1 Day8
9	56 mg BID	5	grade 3 Diarrhea grade 3 Diarrhea and stomatitis (<75% of the total scheduled dose)

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Table 2 B

Treatment-related toxicities occurring in ≥ 10% patients by CH5132799 dose level

Adverse Event	QD														BID						Total (n=38)
	2 mg (n=3)		4 mg (n=3)		8 mg (n=3)		16 mg (n=3)		32 mg (n=4)		56 mg (n=3)		96 mg (n=4)		48 mg (n=7)		56 mg (n=5)		72 mg (n=3)		
Grade	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	
Diarrhea											2		3	2	4		2	2	2		13 (34%)
Nausea	1		1				2		1		1		2	1			3		1		12 (32%)
Stomatitis					1								2		3		4	1	1		11 (29%)
Fatigue	2				1		1		1				1		1		3		1	1	11 (29%)
Rash			1		1						1		2		1		3				9 (24%)
Decreased appetite							1		2				1				2		2		8 (21%)
Vomiting													2				3		1		6 (16%)
Dry skin	1										1		2		2						6 (16%)
Hyperglycemia																1		2		1	5 (13%)
Anemia						1							1			1	1		1		5 (13%)
Abdominal pain											1				1		1			1	4 (11%)

Table 3
Summary of pharmacokinetics of CH5132799 in patients following oral administration

Regimen	Single dose			Repeat dose		***Accumulation ratio
	*AUC_{last} (ng·hr/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	**AUC_{0-24h} (ng·hr/mL)	C_{max} (ng/mL)	
2mg (QD)	53.0(3)	10.0(3)	7.52(3)	48.8(3)	9.92(3)	0.912(3)
4 mg (QD)	112(3)	17.2(3)	8.30(3)	167(3)	22.5(3)	1.54(3)
8 mg (QD)	133(3)	41.1(3)	23.7(3)	159(2)	46.3(2)	1.22(2)
16 mg (QD)	883(1)	113(1)	13.7(1)	621(2)	100(3)	0.972(1)
32 mg (QD)	859(4)	165(4)	12.2(4)	1740(2)	345(3)	1.57(2)
56 mg (QD)	969(3)	163(3)	14.5(3)	748(3)	184(3)	1.07(3)
96 mg (QD)	1650(4)	206(4)	23.2(3)	691(3)	103(3)	0.640(3)
48 mg (BID)	1270(4)	172(5)	10.2(4)	1550(5)**	175(5)	1.10(2)
56 mg (BID)	3030(5)	428(5)	16.3(5)	5940(2)**	331(3)	1.72(2)
72 mg (BID)	2480(3)	265(3)	18.3(3)	5580(1)**	631(1)	2.25(1)

Footnote to Table 2: Mean value and number (noted in parenthesis) are represented for each pharmacokinetic parameter.

* AUC_{last} in single dose represented AUC_{0-72h}.

** AUC_{0-24h} in BID regimen of repeat dose were calculated based on the data from 0 to 12 hours (AUC_{0-12h}).

*** Accumulation ratio represents $AUC_{0-24h/0-12h}$ in repeat dose / $AUC_{0-24h/0-12h}$ in single dose. AUC: area under the plasma concentration time curve, C_{max}: maximum concentration measured, $t_{1/2}$: elimination half-life